140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

Attached hereto are pages entitled "**Version showing changes made to specification**;" a "**Version showing changes made to claims**" and a "**Currently Pending Claim Set.**"

II. REMARKS

Claims 1-4 and 8-15 are presently pending in this application. Claims 4 and 9-14 were withdrawn pursuant to a restriction requirement. Claims 1-3, 8 and 15 stand variously rejected under 35 U.S.C. §§ 103 and 112, first and second paragraphs.

Claim 1 has been amended to specify that the claimed methods are for producing antibodies against a cancer antigen and to specify that the antigen is recognized by an antibody produced by a hybridoma. These amendments are made solely to expedite prosecution, are not intended in any way as an acknowledgment as to the correctness of the Examiner's position, and are made for reasons unrelated to patentability. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

Rejections Under 35 U.S.C.§ 103(a)

Claims 1-3, 8, and 15 stand rejected as allegedly unpatentable over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990). Collectively, Hseih-Ma, Weiner and Ring are referred to as the "primary references." In addition,

claims 1-3, 5-8, and 15 also stand rejected as allegedly obvious over the primary references in view of Fanger or Snider and in further view of U.S. Patent No. 6,054,561.

Applicants traverse these rejections.

It is well settled that even when references relied upon teach that all aspects of the claimed invention are known individually in the art, *prima facie* obviousness is not established without some objective reasoning to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993). Thus, even if individual elements of the invention are taught in the prior art, such is not, in and of itself, sufficient to make out a case of *prima facie* obviousness. See, *Symbol Technologies, Inc. v. Opticon, Inc.*, 19 USPQ2d 1241 (Fed. Cir. 1991) ("We do not pick and chose among the individual elements of assorted prior art references to deprecate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination."). As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."

Moreover, that which is "inherent" in a reference, if not known at the time of the invention, cannot form the basis for rejecting the claimed invention as obvious under section 103. *See, e.g., In re Shetty*, 195 USPQ 753 (CCPA 1977). Thus,

> "The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966).

Applying these rules to the pending case, Applicants submit that the Office has not established that the references teach all the limitations of the pending claims and, in addition, has not established that the references suggest the desirability of the claimed invention. Moreover, the Office has improperly relied on information not known at the time of invention in making this rejection.

As a threshold matter, Applicants note that it is admitted by the Office that none of the primary references disclose, expressly or inherently, methods of inducing antibody production against a cancer antigen using a bispecific antibody. (See, e.g., page 3 of the Office Action). Nevertheless, in the outstanding Office Action, the Examiner repeats the assertion that the secondary references cure these defects by establishing that bispecific antibodies were known to be effective in inducing an immune response.

The law is well-settled that inherency cannot form the basis of an obviousness rejection. *See, e.g., In re Shetty*, 195 USPQ 753 (CCPA 1977). Thus, the Examiner errs in asserting that the secondary references establish that bispecific antibodies were known to induce an immune response to the second antigen. Indeed, until the present application was filed, it was not known that antibodies against cancer antigens could be induced using a bispecific antibody which recognized CD16 and the cancer antigen. (see, specification, page 6, lines 24-28). Nowhere do any of the references report or test antibody production in response to the precisely-claimed subject matter. In sum, the fact that the claimed bispecific antibodies could induce an immune response against the cancer antigen, was unknown prior to Applicants disclosure. Clearly, then, the claimed methods were not known in the art at the time of filing. On this basis alone, an obvious rejection is improper.

Turning to the secondary references specifically, Applicants again note that Fanger and Snider fail to teach or suggest the methods as claimed. Rather, Fanger and Snider are general references describing bispecific antibodies. Neither describe induction of an antibody response to a cancer antigen recognized by the second antibody of the

bispecific antibody. Fanger is silent as to antibody production while Snider discusses antibody responses only in reference to the adjuvanticity of heterocrosslinked bispecific antibodies to enhancing the antibody response to hen egg lysozyme (HEL), not to a cancer antigen. Accordingly, the combination of references set forth in the Office Action does not provide the requisite motivation to arrive at the precisely claimed methods.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The pending claims stand rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite. (Office Action, page 3). In particular, the language of claim 1 was objected to for indicating that an antigen was recognized by a monoclonal antibody produced by a hybridoma. Applicants thank the Examiner for the suggested language and have incorporated the suggestion herein in order to advance prosecution. Accordingly, this rejection has been obviated.

Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner has maintained the rejection of claim 6 under 35 U.S.C. § 112, first paragraph as allegedly lacking written description for failing to meet the deposit requirement. In particular, it is alleged that the text in the specification does not include certain required elements. (Office Action, paragraph 4).

Applicants submit that all of the required elements were present in the declaration submitted January 18, 2001. However, solely in order to expedite prosecution, the specification has been amended herein to include statements allegedly required in the specification itself. Thus, Applicants have fully complied with all the deposit requirements and the rejection of the claims under 35 U.S.C 112, first paragraph, written description should be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-3, 8 and 15 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the claimed invention. In support of this rejection, the Examiner states:

> The specification discloses only a trail in which 11 patients with c-berB-2 overexpressing cancers are administered 2B1, a bispecific antibody known in the art. The specification also includes two examples of induction of an immune response in vitro, using 2B1. The specification does not make or use any other bispecific antibody except for the art known 2B1 antibody. Further, no antibodies "derived from" 2B1 are used, in that no changes in the CDRs of 2B1 are effected, and thus it is not clear that any antibody except for the 2B1 antibody known in the art would function in the instantly claimed methods. (Office Action, page 7).

Because the Examiner has failed to establish a *prima facie* case of non-enablement, Applicants traverse this rejection and its supporting remarks.

Before any analysis of enablement can occur, it is necessary to properly construe the claims. *See, e.g.,* Training Manual on Enablement, page 8. Only when the true scope of the claims is determined can an enablement inquiry begin. The pending claims, when properly read in light of the specification, encompass only bispecific antibodies in which one antibody recognizes CD16, the other recognizes a specifically recited cancer antigen and which induces an antibody response to the cancer antigen. Thus, the scope of the claims is limited as described above.

Once the scope of the claims has been determined, the Office must then review the specification to determine if it teaches one of skill in the art how to make and use the claimed invention without requiring undue experimentation. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). When determining whether the amount of experimentation required is "undue", the courts have determined that "time and difficulty of experiments are not determinative if they are merely routine." (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). In *United States v.*

Telectronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989), the Federal Circuit ruled that a specification setting forth one working embodiment and a method of testing other embodiments was enabling, even in the face of evidence that testing for other suitable embodiments would require approximately $50,000 and 6-12 months. (see, also, Training Manual on Enablement, page 31).

Further, Applicants are under no legal obligation to teach or exemplify each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and Trademark Office's Training Materials on Enablement, p. 29. Thus, the presence of only one working example should never be the sole reason for making a scope rejection. *Id.* at 27. In sum, the standard for determining enablement is not what the prior art alone predicts, but, rather, what Appellants' specification (in view of information known in the art) actually teaches one of skill in the art.

In the pending case, the Office has not established a *prima facie* case of non-enablement. Rather, this rejection is improperly based on the following lines of reasoning: (1) only two working examples are presented; (2) various references establish unpredictability; and (3) the specification does not provide guidance. (Office Action, page 7). These arguments cannot support a case of non-enablement. First, as noted above the presence or absence of working examples is but one factor to consider.

Second, with regard to the references, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). The state of the art is judged at the time the application was filed -- in this case December 2, 1994. All of the references cited by the Examiner were published well before the filing date of the present

application and, therefore, are not reasonably indicative of the state of the art at the time of filing.

Furthermore, the relevant art is defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc., for which the invention is used. *See, e.g.,* PTO Training Manual on Enablement, page 15. Upon careful review, it is clear that the references cited by the Office, namely, Rudikoff (1979), Adair (1990), Panka (1988) and Amit (1986) are not relevant art.

The Examiner's position regarding the references appears to be that virtually any reference tangentially related to antibodies is relevant to the claimed immunoassay methods. This reasoning is entirely improper. None of the references cited by the Examiner address methods of inducing an immune response to the cancer antigen recognized by the second antibody of a bispecific antibody. Accordingly, on this basis alone, none is relevant. Even assuming for the sake of argument only, that the references were relevant, Applicants note that methods for testing suitable bispecific antibodies to determine whether they induce an immune response are set forth in the specification, for example on page 15 (describing production of antibodies) and pages 24 to 26 (describing techniques for determining induction of an antibody response following administration of a bispecific antibody). Therefore, although the references are not relevant to the claimed invention, the specification effectively rebut any argument that practicing the claimed methods requires undue experimentation.

Lastly, with regard to the third point, the Examiner is reminded that the law regarding enablement makes it clear that without a reason to doubt the truth of the statements made in the application, the application must be considered enabling. *See, e.g., In re Wright,* 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Here, the specification teaches how to make bispecific antibodies, including altered antibodies and how to test these antibodies for their ability to induce antibody production against a cancer antigen.

(See, *e.g.*, pages 12-15 and pages 24-26). Further, the specification clearly identifies what the methods entail:

> ...administration of bispecific antibodies which recognize and bind FcgRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen. The second antigen can be present on the surface of cells and be a self antigen, including cancer antigens. (page 6, lines 24 to 28)

Thus, contrary to the Office's assertion, the specification does in fact provide sufficient guidance to allow one of skill in the art to practice the methods as claimed. Accordingly, a *prima facie* case of non-enablement has not been made out by the Office.

In view of the lack of a *prima facie* case of non-enablement, Applicants are not required to come forward with factual evidence or examples that predicts, *a priori*, if any given bispecific antibody would induce an immune response to the antigen recognized by the second antibody of the bispecific antibody. However, the present record is replete with representative examples and statements applicable to the genus as a whole. The specification teaches how to make suitable bispecific antibodies (pages 10-16). Applicants plainly teach a skilled artisan to test whether a specific bispecific antibody induces an immune response to the proper antigen. (See, Examples). Each of these procedures is well within the capabilities of one skilled in the art. Thus, in light of the guidance provided by the specification, the skilled artisan could readily perform the methods of the claimed invention.

In sum, the enablement requirement is satisfied and Applicants respectfully request these rejections be withdrawn.

III. CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect.

Atty Docket No.: 2300-0999
USSN: 08/349,489
PATENT

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Respectfully submitted,

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Version Showing Changes Made to Specification

On page 29, following the paragraph beginning on line 26:

As described above, cell lines for 2B1 (CRL 10197), 1A7 (HB 10501), and 520C9 (HB 8696) have been deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209. The ATCC accession numbers for the both antibodies disclosed herein are 452F2 (HB 10811), 741F8 (HB 10807), 520C9 (HB 8696), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB10812), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB10801), 42E7 (HB11751), 388D4 (HB 10794), 42H8 (HB 11830), 35E6 (HB 11769) and 36H3 (HB 11768). The cell lines will be maintained at the named depository for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited cell lines was received by the depository and, in any case, for a period of at least thirty (30) years after the date of the deposit, or during the enforceable life of the patent, whichever is latest, and the cell lines will be replaced should the cell lines become non-viable. All restrictions on the availability to the public of the cell lines will be irrevocably removed upon the granting of any patent issuing on this application for patent.

Version Showing Changes Made to Claims

IN THE CLAIMS

Please amend the claims as follows:

1. (Amended) A method of inducing production of antibodies against a cancer antigen [an immune response in a patient], comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcgRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

Currently Pending Claims

1. (Amended) A method of inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcgRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

2. The method according to claim 1, wherein said first binding site is a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma.

3. The method according to claim 1, wherein said second antigen is present in the patient.

8. The method according to claim 1, wherein said bispecific antibody is produced by the hybrid hybridoma CRL 10197.

15. The method according to claim 1, wherein said second antigen is not present in the patient upon first administration of the bispecific antibody.